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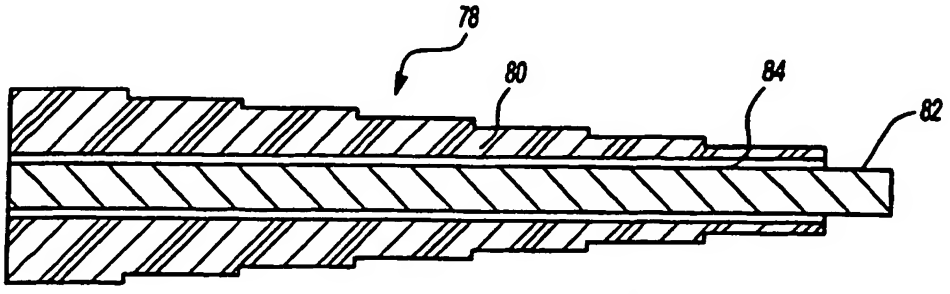
(54) Title: SUSTAINED RELEASE OPHTHALMOLOGICAL DEVICE AND METHOD OF MAKING AND USING THE SAME



(57) Abstract: An ophthalmological implant and method of making and using the same. One preferred implant (78) is prepared to include an implant member (82). A region (84) includes a pharmaceutical agent and an overlying barrier layer (80) of a bioerodible

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Sustained Release Ophthalmological Device and Method of Making and Using the Same

Claim of Benefit of Filing Date

The present application claims the benefit of the filing date of United States Provisional Application Serial Nos. 60/349,465, filed January 18, 2002, and 60/397,698, filed July 22, 2002, the contents of which are hereby incorporated by reference for all purposes.

Technical Field

The present invention relates to ophthalmologic implants and more particularly to implants that incorporate a sustained release pharmaceutical agent, such as a steroid, an antibiotic, an anti-inflammatory agent, antiglaucomatous, or a combination thereof.

Background of the Invention

Currently available delivery systems for intraocular therapeutics are generally limited to 1) drops, which carry issues of expense, inconvenience, patient noncompliance (by overuse, underuse, or inappropriate frequency of use) as well as difficulty for delivery of the medications by certain patients (especially those with arthritic conditions who cannot manipulate the vials properly); 2) injections; and 3) bulky intravitreal implants placed within the vitreous cavity of the eye, requiring incisions in the eye and delicate manipulations of the vitreous gel .

There is a need to provide an efficient technique and device for introducing a pharmaceutical agent into the eye, particularly for sustained release following a surgical procedure. In another aspect, there is a need to provide an effective and convenient mechanism to deliver antibiotics, anti-inflammatory, antiglaucomatous, or other pharmaceuticals to the intraocular environment for therapeutic and prophylactic purposes, particularly following cataract or clear lens removal surgeries.

a) a filament configured for insertion into an eye;

b) a first layer including a pharmaceutical agent;

c) a second layer of variable thickness overlying the first layer and including a sustained release medium material selected from a bioerodible material, a biodegradable material, a bioavailable material or a mixture thereof, the second layer being dimensioned for prolonged release of the pharmaceutical agent from the ring as the second becomes smaller.

In another alternative preferred aspect, the present invention contemplates a method for making an ophthalmologic implant comprising the steps of:

a) providing a filament configured for insertion into an eye as an ophthalmologic implant selected from an endocapsular tension ring or an intraocular lens;

b) attaching a first layer including a pharmaceutical agent to the filament; and

c) attaching a second layer of variable thickness over the first layer, the second layer including a sustained release medium material selected from a bioerodible material, a biodegradable material, a bioavailable material or a mixture thereof, and the second layer being dimensioned for prolonged release of the pharmaceutical agent from the filament as the second layer becomes smaller.

The present invention contemplates not only methods of making ophthalmologic implants, but methods of implanting the implants into an eye (e.g., a human, a dog eye, horse eye or the like), therapies that employ the use of such an implant in an eye, as well as the implants themselves. The present invention affords numerous advantages including the elimination of a need for an implant recipient to receive prolonged post-operative therapy with topically applied pharmaceutical agents. In turn, this will help reduce post-operative prescription drug costs, and associated health care needs.

Existing commercially available implants may be employed, or custom designed ones may be employed. In either case, the structure of the implant may be varied as desired for accommodating the pharmaceutical agent, such as by modifying the structure for increasing available surface area per unit volume. For example, in another preferred embodiment, a component of an implant (e.g., the filament) has wells, divots, pores, grooves, or other crevices for containing the pharmaceutical agent on one or more sides of the filament. The wells, divots, pores, grooves, or other crevices may vary in size, depth, or number along the length of the filament so as to correspond to a desired dosing regimen of the agent(s) over time. A variety of axial cross-sectional or longitudinal configurations could achieve similar results, including but not limited to spiraling, rifling, fluting, stippling, or dimpling. The surface of the implant may also be treated such as by surface roughening (e.g., mechanically, chemically or a combination thereof), a primer or other coating, or a combination thereof. The surface of the implant might be crosslinked with a pharmaceutical compound or moiety, or a polymer or oligomer containing the same.

In one embodiment, it is contemplated that the pharmaceutical agent is supported or carried by a porous structure. Such a structure may be made by producing a mixture that includes at least one porogenic agent, compacting or shaping the mixture to its desired form, and heating or otherwise treating (e.g., by solvent) the product obtained in such a way that the porogen is removed. At least one pharmaceutical agent may be incorporated in the pores where the porogenic agent used to be.

In another embodiment, the pharmaceutical agent may be applied in a first state and reacted or otherwise transformed to form a second state. For instance, an implant may be dipped in a pharmaceutical agent and then irradiated, heated or otherwise treated.

When the implants are coated, in accordance with any of the processing steps herein, they may be coated by a suitable coating technique, including (by way of example, without limitation, spraying, dipping, swabbing, brushing, rolling, curtain coating, doctor blading, vapor deposition or combinations thereof.

member, a plate (e.g., a plate haptic configuration), a radial support member, a pararadial support member, a tangential support member, a circumferential support member, or a combination thereof.

The gross shape of the implant is such so as to be readily placed within an eye. By way of example, an endocapsular tension ring is configured so as to be positioned within the fornix of the capsular bag, as is typical with the known standard endocapsular tension rings. The implants may be made of any suitable material, e.g., a plastic material such as poly(methylmethacrylate) or other acrylic, preferably for affording some flexibility with the gross structure of the implant.

Among the many alternative configurations of the present invention, examples of combinations contemplated by the invention include:

1) A member with a hollow core in which a pharmaceutical agent, sustained release pharmaceutical agent or medicinal material is impregnated into the core, pores or crevices on a surface of the member, or coated pharmaceutical agent could be pre-loaded (either by manufacture or postmanufacturing preparation) or placed intraoperatively. The aqueous material of the eye could percolate or flow through the cavity via openings at either ends, channels, grooves, fenestrations, or other openings between the central core and the outer wall.
2) A ring with a solid or hollow composition with one or more elements, grooves, or other modifications of the ring which affix or allow the fixation of a pharmaceutical agent, sustained release pharmaceutical agent or material impregnated with a pharmaceutical agent, whether in the form of a filament, aggregate, film, or other geometric or non-geometric configuration; or
3) A ring composed of pharmaceutical agent, sustained release pharmaceutical agent or biodegradable material impregnated pharmaceutical agent.

A ring as described above could be designed for fixation within the ciliary sulcus or pars plana of the eye either by passive means or suture fixation to the eye.

To illustrate, in one highly preferred embodiment, an implant member would be placed on a suitable surface, e.g., a substantially planar surface, and one or more pharmaceutically active agents would be sprayed, swabbed, brushed, vaporized, dipped or otherwise coated continuously, intermittently, uniformly or non-uniformly, entirely or partially onto the exposed surface of the filament and allowed to dry, polymerize, crystallize, or otherwise adhere or attach. The implant could be turned over, exposing the previously downfacing, protected surface. Another application of the same or other pharmaceutical agent(s) or admixture of agents would be similarly applied to the now upward, exposed surface and similarly allowed to dry, polymerize, crystallize, or otherwise adhere or attach. The filament could then be weighted at an end or otherwise drawn into a straight, hollow tube, effectually straightening out the ring-shaped native configuration of the filament. The sustained release medium material could then be applied in a uniform, tapered, or stepwise tapered fashion by either serial dipping, at varying locations along the length of the straightened complex, immersion with a varying time of immersion for varying portions along the length of the implant within a fluidic medium including the sustained release medium as to predicatably vary the thickness of the sustained release medium along the length of the implant. Alternatively, the tube could act as a mask so that the sustained release medium could be applied in varying thicknesses by varying the amount of the length of the implant exposed for varying duration of time while by being sprayed, swabbed, brushed, vaporized, sputtered, dipped or otherwise coated.

An another highly preferred embodiment, the implant could be coated, as described above, or otherwise, with one or more layers of one or more admixtures of a degradeable layer, such as a layer that includes a bioerodable agent and/or a pharmaceutical agent(s). For example, one or more initial coats of a sustained release medium may include pharmaceutical agent(s) with or without steroid, properties, while one or more subsequent outer coats of another admixture might include pharmaceutical agents with or without steroid antimicrobial properties. This type of configuration would have the effect of delivering antimicrobial and anti-inflammatory agents first, then

3) Non-steroidal anti-inflammatory drug (NSAID) : Released at gradually taper dosage over approximately 28-40 days.

Other agents may be desired in some cases or as newer pharmaceuticals become available.

The particular bio-compatible material for use as a sustained release medium may be selected as desired. Such material may be provided for securing onto an ophthalmologic implant in a form selected from a liquid, a powder, a gel, or a mixture thereof. Solid materials may be crystalline, amorphous, or a mixture thereof, either in their as provided state or in an intermediate or final state. The material may include or consist essentially of a small molecule, an oligomer, a polymer (organic, biological or a combination thereof), or combinations thereof. Preferably the material is of one or more pH levels that are compatible with an eye.

The specific material may vary. Examples of materials that may be employed for providing a sustained release include, without limitation, caprolactones (e.g., a polyactide-coglycolide-co-caprolactone (PGLC) polymer), multivesicular liposomes (e.g., with unilamellar vesicles, mutilamellar vesicles, neosomes, closely packed non-concentric vesicles (such as DEPOFOAM™), or combinations thereof), salts (e.g., an ammonium salt of 1-0- hexadecylpropanediol-3-phospho-ganiclovir (HDP-P-GCV)), poly(lactic acid), poly (glycolic acid), copolymers of lactic and glycolic acids, poly (DL-lactide-co-glycolide) (PLGA) or blends of PLGA of different molecular weights, poly (orthoester), acrylic polymers, methacrylic polymers, poly (hydroxyethylmethacrylate), polysulfone or mixtures thereof. The present invention contemplates that the material employed may be one that is not listed herein and the omission from the above list should not be construed as limiting of the scope of the invention.

It is contemplated that a suitable material for delivering a pharmaceutical agent might include a material that releases the agent over time through or as a result of diffusion, chemical reaction, ion exchange, degradation or combination thereof.

The materials may comprise microspheres, microparticles, other vesicles, capillaries, combinations thereof, or other forms.

The medicinal materials of the present invention may also be included on other surgical supplies for use in an eye, such as sutures or surgical instruments.

The implants of the present invention may be permanent or temporary. Accordingly, the methods herein also contemplate performing a subsequent removal, replacement, or both, of an implant. While it is typical that many of the implants herein will be employed for a single use and then disposed of, it is also possible that implants may be removed and re-used (including a possible step of re-treating the implant for adding more pharmaceutical agent. Removal and replacement of on implant on a periodic basis is thus contemplated, either at regular intervals of similar amounts of time or at different amounts of time.

Turning now to examples of different structural embodiments, reference is made to the drawings. Various other embodiments will be apparent as well from a review of the drawings, which are not intended as limiting. For example, in some drawings, it is illustrated that the outer layer is generally tapered. It need not be, but can be of constant cross section. For example, there can be different thicknesses of barrier layer, pharmaceutic agent layer, the implant or a combination thereof over discrete locations along the implant. Further, the respective consecutive doses need not be adjacent to one another but can be staggered over the length of the filament. The corners of the coatings that correspond to the respective doses that are depicted in the drawings herein may also be smooth curves. The implant may also be structured as a helical or with threads for varying its surface topography.

Fig. 1 shows an intraocular lens (IOL) 10 that may be treated in accordance with the present invention. The IOL 10 includes a lens portion 12 and one or more haptics 14. Examples of various other IOL configurations can be gleaned from U.S. Patent No. 6,352,542, and the art cited therein, hereby expressly incorporated by reference.

Figs. 2-4 illustrate examples of a first endocapsular tension ring 18, a second endocapsular tension ring 20, and a third endocapsular tension ring 24, all including positioning holes at their ends. From Fig. 3, it is seen that

type of Fig. 6. In this embodiment, an aperture 50 may be defined in the plate portion 52 onto which a filament, ribbon, film, cord, or other member may be inserted, coated, bonded or otherwise attached or affixed.

The embodiment of Fig. 9 likewise may be used alone or in combination with one or both of the embodiments of Figs. 7 and 8.

Turning now to Figs. 10-13, there are shown alternative approaches for treating a thin member, such as a haptic (e.g., wire or plate) an endocapsular tension ring or other structure for carrying a pharmaceutical agent.

In Fig. 10, showing a view in cross-section, member 56 includes passages 58 in communication with a central passage into which a pharmaceutical agent 60 may be introduced.

In Fig. 11, a member 62 includes opposing spaced ends 64 and 66 and an opening for receiving a pharmaceutical agent 68. The agent 68 is released through an opening 70 defined by the ends 64 and 66, which may be a hole, a channel or otherwise.

In Fig. 12, there is seen an approach wherein an implant is laminated to include a member 72 having a layer 74 with a pharmaceutical agent attached thereto.

Fig. 13 shows yet another alternative, pursuant to which a member 76 is coated over at least a portion, if not substantially the entirety of its outer surface with a layer 78 including a pharmaceutical agent.

The embodiments illustrated in Figs. 7-13 are not intended as limited to the employment of a pharmaceutical agent dispersed or otherwise carried in a matrix of a suitable pharmaceutical carrier. As the discussion of Figs. 14-28 will demonstrate, and as discussed herein, other layers or combinations are possible.

For example, the various embodiments of Figs. 14-28, illustrate the concepts discussed herein of employing a barrier layer that will diminish over time for exposing a thereby releasing pharmaceutical agent. The barrier layer may be smooth, or irregular (e.g., stepped, jagged, or otherwise) over some or all of its outer surface, inner surface or combination thereof. Preferably, the barrier layer overlies a layer of pharmaceutical agent, which in turn is disposed on or within an implant member, that effectively is a core of the

implant member 120 having first wells 122 and second wells 124. The first wells 122 may extend over a different length of the implant member 120, so that after a period of time only the pharmaceutical agent of the first wells is released.

The embodiments of Figs. 21 and 22 illustrate yet another alternative employing a pharmaceutical agent region 126, a barrier layer 128 and implant member 130. In this aspect, at least first well 132, second well 134 and third well 136 are staggered in partially overlapping relation to each other where the second well spans at least the length between the first well 132 and third well 136, for helping to assure more continuous and less episodic release of the pharmaceutical agent.

The embodiments of Figs. 23 and 24 show yet another alternative embodiment, in which well sizes are varied for receiving different volumes of pharmaceutical agent. Thus a barrier layer 138 over a pharmaceutical agent region 140 can be configured on an implant member 142 so that (as seen from the top view of Fig. 24), a wall 144 defines first, second and optionally third wells 146, 148 and 150.

Instead of varying the length of the well, it is also possible to vary its height. Moreover, as appreciated, the barrier layer of each of the embodiments shown need not be stepped or irregular, but may be smooth and continuous of constant thickness, sloping thickness.

To illustrate, Fig. 25 shows an embodiment that has a smooth sloping barrier layer 152. As seen in Fig. 26, a suitable pattern 154 of wells for the pharmaceutical agent may be employed if desired such as described previously. The pattern may be selected as desired.

Fig. 27 illustrates yet another alternative in which an implant member 156 is generally smooth over its outer surface. Pharmaceutical agent is applied to define raised regions 158 over which a barrier layer 160 is applied. The thickness of the barrier layer may vary along the length 20 that as the thickness diminishes over time, only certain regions 158 will become exposed. Thus it is possible that there can be simultaneous exposures of pharmaceutical agent along substantial portions of, if not the entirety of the length of the implant.

embodiments, for any given application. It will also be appreciated from the above that the fabrication of the unique structures herein and the operation thereof also constitute methods in accordance with the present invention.

It is understood that the above description is intended to be illustrative and not restrictive. Many embodiments as well as many applications besides the examples provided will be apparent to those of skill in the art upon reading the above description. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references, including patent applications and publications, are incorporated by reference for all purposes.

9) The method of any of claims 1 through 8, further comprising the step of providing the implant, having the sustained release medium and the pharmaceutical agent applied thereto, to a health care provider for performing cataract surgery.

10) The method of any of claims 1 through 9, wherein the implant is fabricated from polymethylmethacrylate.

11) The method of any of claims 1 through 10, wherein over a major portion of its length, the outer surface of the implant, having the sustained release medium and the pharmaceutical agent applied thereto, is selected from a smooth surface an irregular surface, a stepped surface, a tapered surface, a surface having no slope or a combination thereof.

12) The method of any of claims 1 through 11, wherein at least one of the sustained release mediums, the pharmaceutical agent, or a combination of both, is applied to the implant by a step including, spraying, dipping, swabbing, brushing, rolling, curtain coating, doctor blading, vapor deposition or combinations thereof.

13) A device provided according to any of the claims 1 through 12.

14) A therapy employing a device prepared according to any of claims 1 through 13.

15) The method of any of claims 1 through 14, wherein the pharmaceutical agent is applied to the implant along the length of the implant as a continuous layer or an intermittent layer.

16) The method of any of claims 1 through 12, wherein the pharmaceutical agent is applied to the implant by producing a mixture that includes at least one porogenic agent, compacting or shaping the mixture to its desired form, treating the product obtained in such a way that the porogen is removed, and introducing pharmaceutical agent where the porogen used to be.

17) The method of any of claims 1 through 12 or 15-16, further comprising the step of implanting the implant into an eye of a human, a dog or a horse.

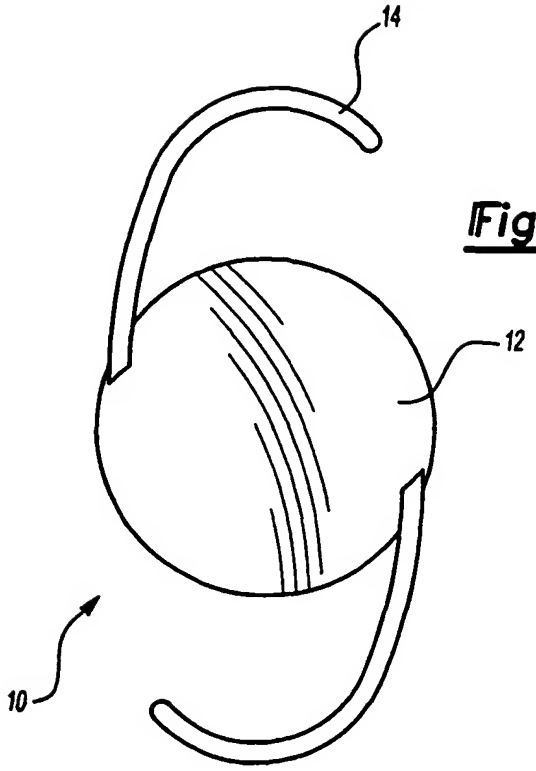

Fig-1

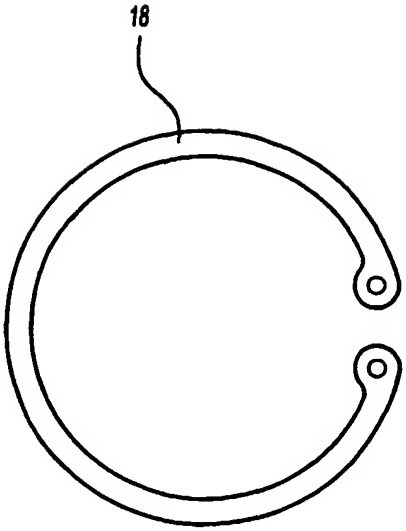

Fig-2

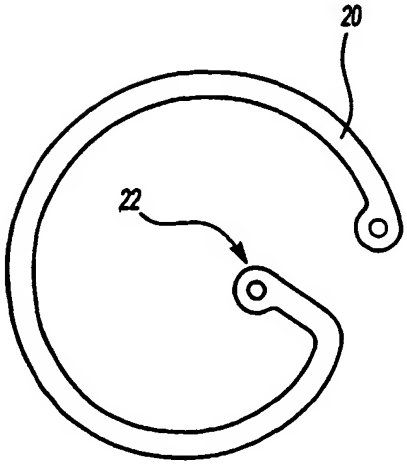

Fig-3

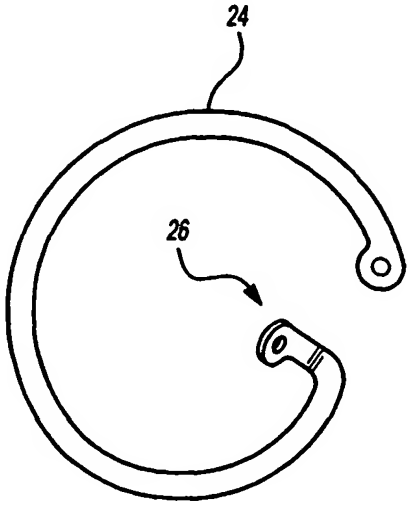

Fig-4

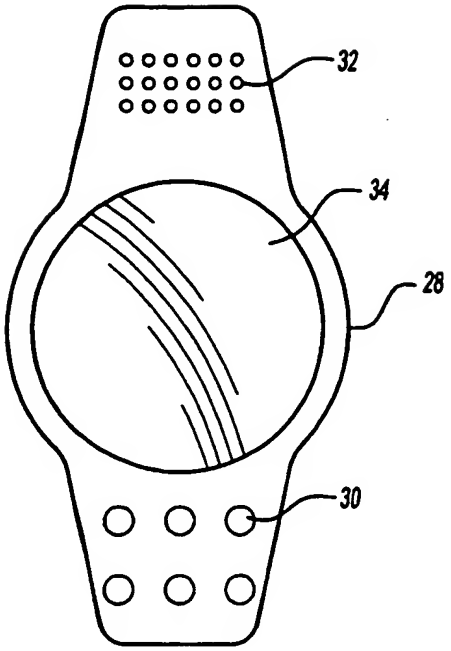

Fig-5

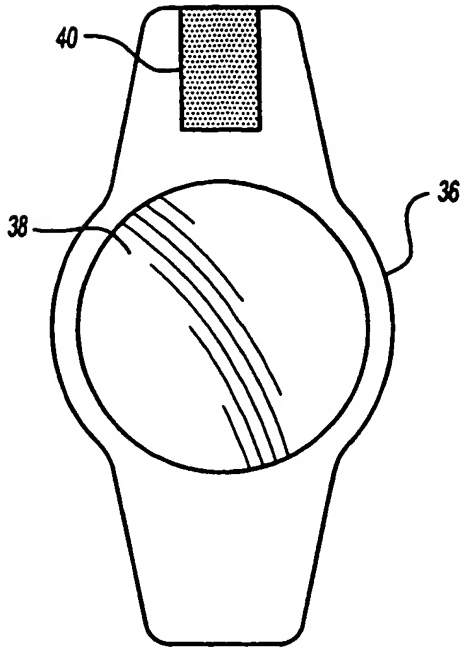

Fig-6

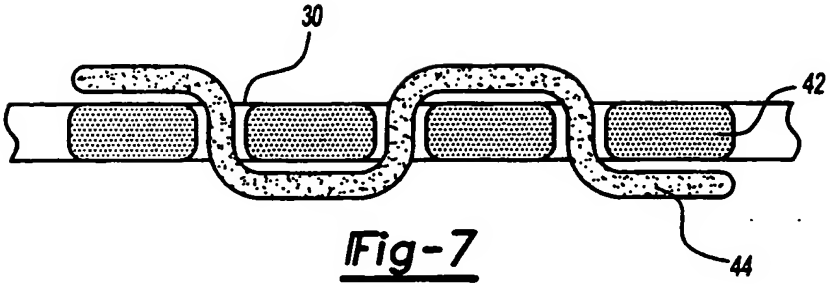

Fig-7

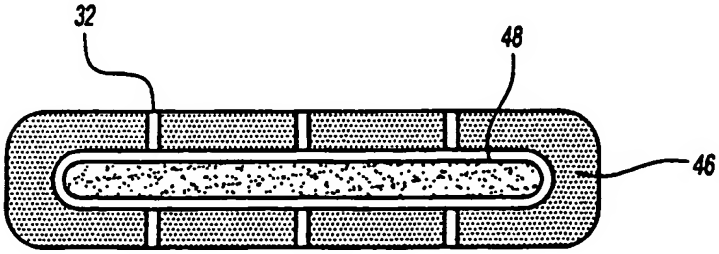

Fig-8

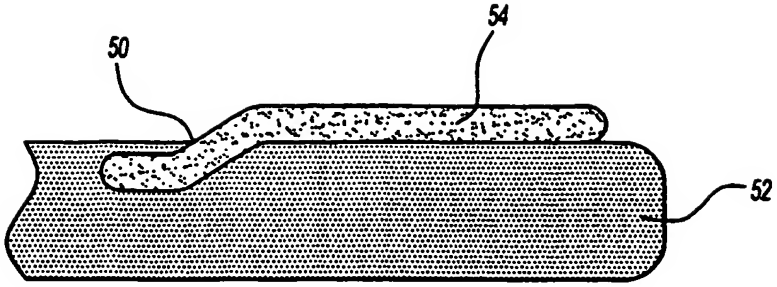

Fig-9

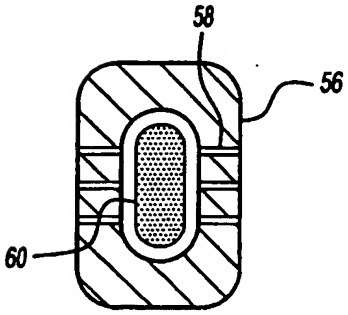

Fig-10

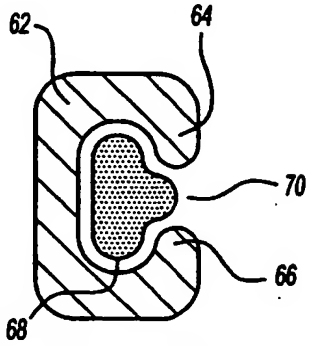

Fig-11

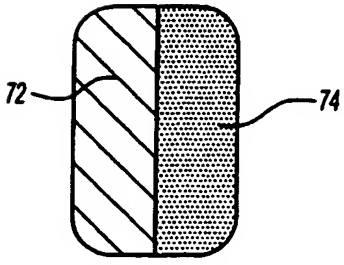

Fig-12

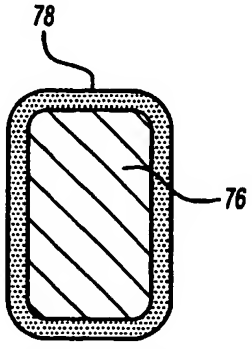

Fig-13

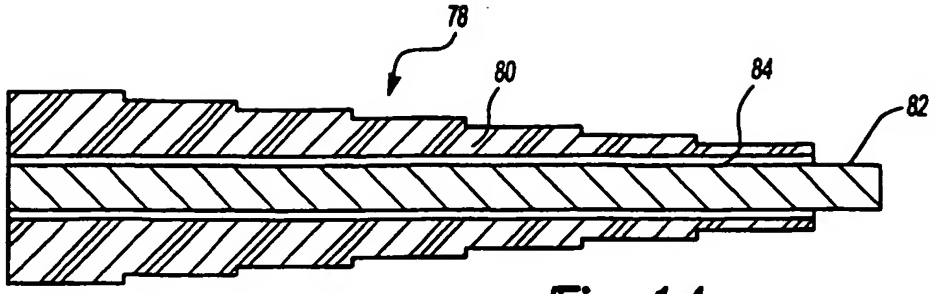

Fig-14

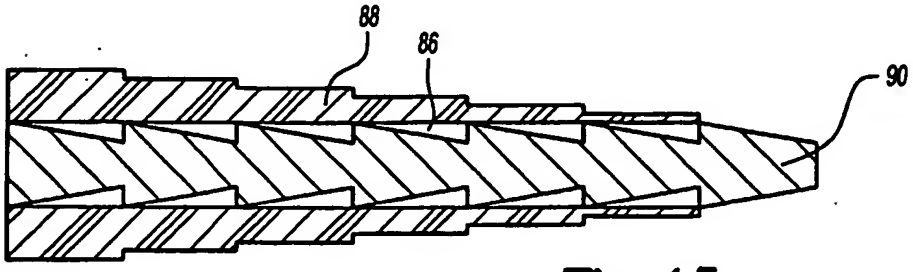

Fig-15

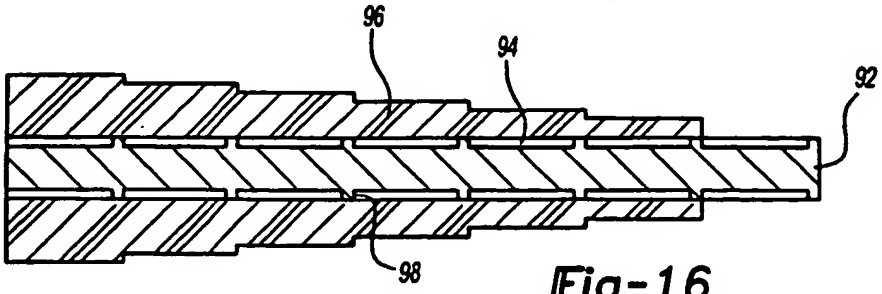

Fig-16

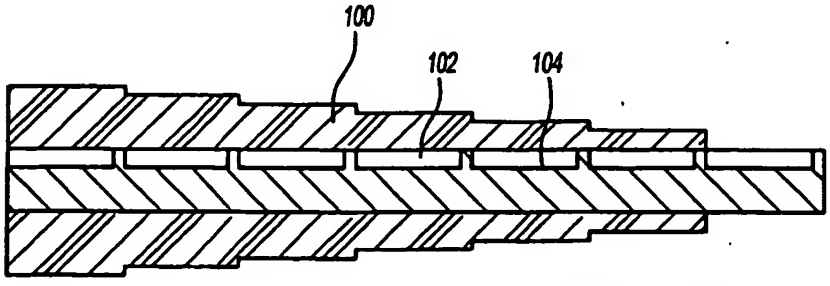

Fig-17

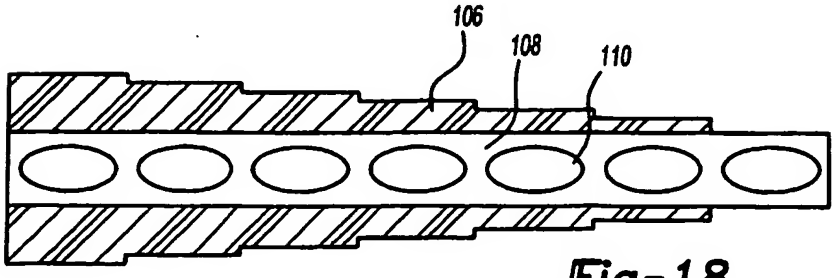

Fig-18

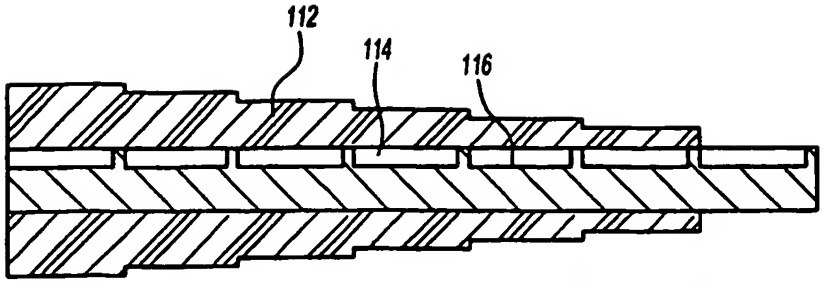

Fig-19

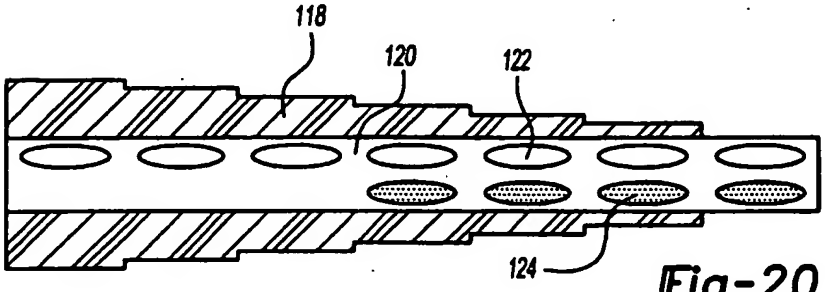

Fig-20

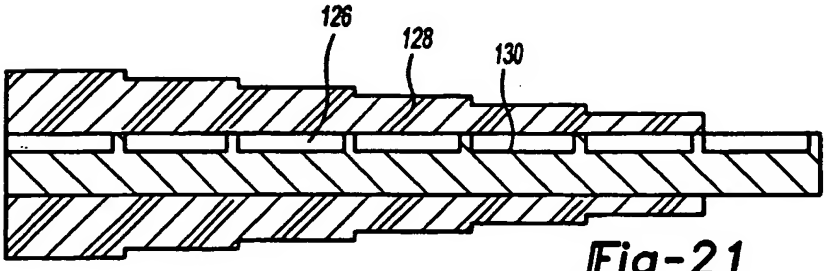

Fig-21

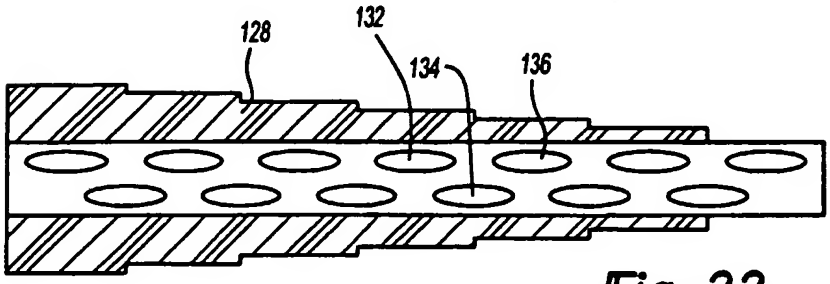

Fig-22

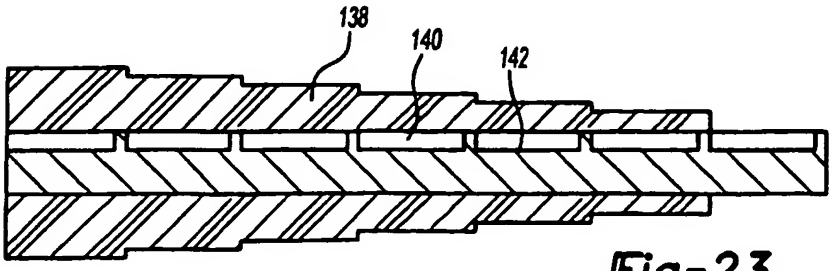

Fig-23

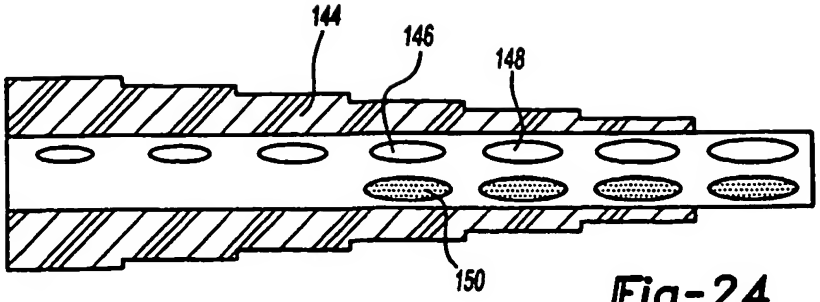

Fig-24

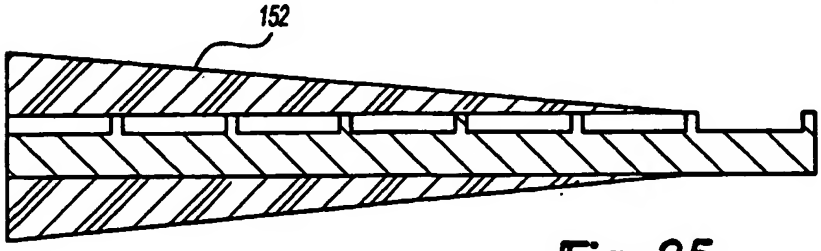

Fig-25

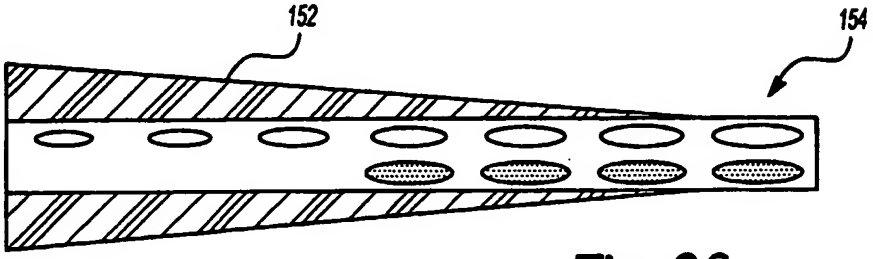

Fig-26

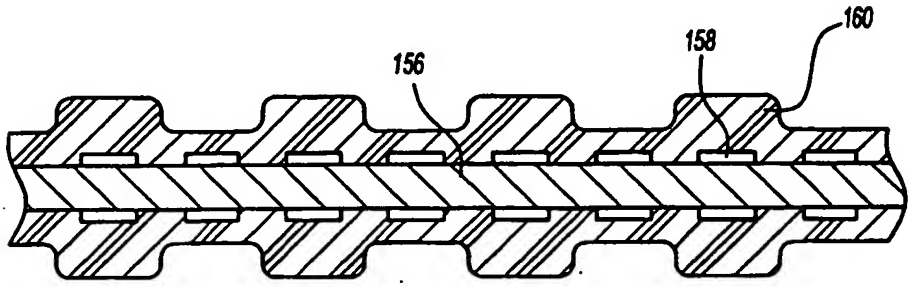

Fig-27

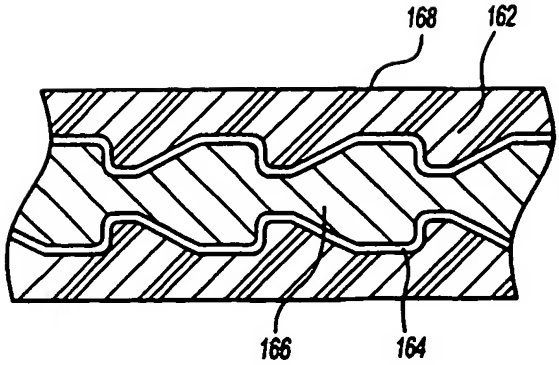

Fig-28